REMARKS

Upon entry of this amendment, claims 7, 24 and 25 will be pending and under consideration.

Claim 7 has been amended to delete the term "or a derivative thereof" and to specify that the individual is a human individual in order to more clearly claim the invention described in the specification and claims as originally filed. Support for the amendment to claim 1 is found at page 20, line 21. No new matter is added.

Rejection under 35 U.S.C. § 112, First Paragraph

Claims 7, 24 and 25 are rejected under 35 U.S.C. § 112, first paragraph, allegedly, since the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention. According to the Examiner, it would require undue experimentation to practice the claimed invention.

Applicants respectfully disagree. Applicants incorporate their remarks of the last amendment by reference herein and address certain points raised by the Examiner. Preliminarily, Applicants note that claim 7 had been amended to recite a method to increase production of at least one Th1 cytokine or to decrease production of at least one Th2 cytokine in an individual free of infection with an immunodeficiency-type retrovirus comprising administering an effective amount of a peptide selected from the group consisting of peptides comprising the amino acid sequence Cys Lys Pro Ile Ser Gly His Asn Ser Leu Phe Trp Tyr Arg Gln Thr (SEQ ID NO:1) to an human individual free of infection with an immunodeficiency-type retrovirus in an amount sufficient to increase production of at least one Th1 cytokine or decrease production of at least one Th2 cytokine.

With regard to certain statements of the Examiner set forth in the Section 112 rejection, Applicants point out the following.

On page 3 of the Office Action mailed November 5, 2003, the Examiner states that the disclosure fails to provide any guidance pertaining to the location of the TCR peptide within the context of the larger receptor. Applicants note that this information is known in the prior art. For example, the Examiner's attention is invited to the background section of the present specification on page 3, lines 14-21, wherein the peptide of SEQ ID NO:1 recited in claim 7 of the instant application is discussed with regard to U.S. Patent No. 5,911,990 to Marchalonis *et*

al. In column 2, lines 45-47 of U.S. Patent No. 5,911,990, it is taught that the peptide corresponds to the first complementary determining region of the T-cell receptor Vβ domain.

With regard to the Examiner's statement on page 3 that the claims of the present application are "extremely broad and encompass numerous species (*i.e.*, any derivative of SEQ ID NO:1)", Applicants note that claim 7 has been amended such that derivatives of the peptide are no longer encompassed in the claim.

With regard to the Examiner's statement on page 4 of the Office Action that Applicants have not addressed any of the Examiner's concerns, Applicants note that the Examiner's concerns are not legally sufficient to support a lack of enablement rejection. The Examiner's "concerns" are merely unfounded and unsupported allegations. Applicants remind the Examiner again that the invention cannot be questioned on the unsupported skepticism of the Examiner. *Ex parte Linn*, 123 U.S.P.Q. 262 (PTO Bd. Pt. App. Int. 1959); *Ex parte Rosenwald*, 123 U.S.P.Q. 261 (PTO Bd. Pt. App. Int. 1959) (emphasis added).

With regard to the Examiner's statement on page 7 that the claims are of considerable breadth and encompass the treatment of any solid tumor, any cardiovascular disorder, any allergic disorder, and the progression to AIDS employing the claimed peptide, Applicants submit that the Examiner is improperly imparting limitations into the claims from the specification. Claim 7 is directed to a method to increase production of at least one Th1 cytokine or to decrease production of at least one Th2 cytokine in an individual free of infection with an immunodeficiency-type retrovirus comprising administering an effective amount of a peptide selected from the group consisting of peptides comprising the amino acid sequence Cys Lys Pro Ile Ser Gly His Asn Ser Leu Phe Trp Tyr Arg Gln Thr (SEQ ID NO:1) to an human individual free of infection with an immunodeficiency-type retrovirus in an amount sufficient to increase production of at least one Th1 cytokine or decrease production of at least one Th2 cytokine. All that the claim requires is that production of at least one Th1 cytokine is increased or production of at least one Th2 cytokine is decreased in the human individual.

There is no requirement or limitation in the claim that any of the foregoing diseases are treated. It is well settled law that the claims define the invention and that the claim language is to be measured for patentability, not the specification. See M.P.E.P. § 904.01, which states that "[t]he breadth of the claims in the application should always be carefully noted; that is, the examiner should be fully aware of what the claims do *not* call for, as well as what they do require." (emphasis in original). Claims that were pending and directed to treating such disorders have been canceled without prejudice in the present application due to their

withdrawal from consideration in view of a restriction requirement. Although Applicants have reserved their rights to pursue the canceled claims in a related application, their patentability, including their enablement, is a question for that related application, not this application.

Additionally, the Examiner's attention is invited to U.S. Patent No. 5,911,990 to Marchalonis *et al.*, (Reference AA, of record), which clearly teaches that administration of the peptide of SEQ ID NO:1 to a mouse suffering from murine AIDS is able to restore normal levels of Th1 and Th2 cytokines (see Abstract). The Examiner's attention is also invited to Sepulveda *et al.*, 2003, J. Cardiovasc. Pharmacol. 41:489-497, ("Sepulveda I", Reference AF, made of record in the Supplemental Information Disclosure Statement submitted concurrently herewith). Sepulveda I also teaches that administration of the peptide of SEQ ID NO:1 to a mouse infected with LP-BM5 results in a longer progression time to mADIS by increasing production of at least one Th1 cytokine is increased or decreasing production of at least one Th2 cytokine. Further, in mice infected with both LP-BM5 and with coxsackievirus CVB3, which leads to myocarditis, Sepulveda I discloses that administration of the peptide of SEQ ID NO:1 provides a protective effect against the development of said myocarditis. See Sepulveda I, page 7, left column. Thus, a nexus between increasing production of at least one Th1 cytokine is increased or decreasing production of at least one Th2 cytokine and AIDS and/or cardiovascular disease in an animal infected with an immunodeficiency-type retrovirus has been conclusively shown by Applicants.

The Examiner's attention is also invited to Sepulveda *et al.*, T-Cell Receptor Vβ8.1 Peptide Reduces Coxsackievirus-Induced Cariopathology in Aged Mice, ("Sepulveda II", manuscript in preparation and attached hereto as Exhibit A). Sepulveda II discloses that mice not infected with an immunodeficiency-type retrovirus, but infected with a coxsackievrus develop cardiopathology. However, administration of the peptide of SEQ ID NO:1 not only resulted in the increased production of at least one Th1 cytokine but also inhibited or reduced coxsackievirus-induced cardiopathology. Thus, in an animal free of an immunodeficiency-type retrovirus, the peptide of SEQ ID NO:1 increased production of at least one Th1 cytokine and provided a cardio-protective effect.

In view of the foregoing, Applicants submit that the claimed invention is fully enabled and meets all the requirements of Section 112, first paragraph. Therefore, Applicants respectfully request that this Section 112 rejection be withdrawn.

CONCLUSION

Applicants respectfully request that the above-made amendments and remarks of the present response be entered and made of record in the file history present application. Applicants submit that presently pending claims 7, 24 and 25 meet all requirements for patentability and respectfully request allowance and action for issuance.

Applicants request that the Examiner call the undersigned at (212) 790-9090 if any questions or issues remain.

Respectfully submitted,

Date: December 5, 2003

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Enclosures

T-Cell Receptor Vβ8.1 Peptide Reduces Coxsackievirus Induced Cardiopathology in Aged mice.

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Abstract

Immunosenescence is characterized by a dramatic reduction in responsiveness as well as functional dysregulation. These changes in the immune system render the host susceptible to develop an array of conditions like: cancer, autoimmune and infectious diseases. One of the arms of the immune system that is considerably affected by age is the adaptive immune response, specifically T and B-lymphocytes. Viral myocarditis is an important cause of heart failure and dialated cardiomyopathy. The Global Surveillance of Virus Diseases program of the WHO ranks coxsackievirus B as the number one viral agent causing cardiovascular disease. TCR Vβ 8.1 peptide a 16-mer peptide containing the entire CDR1 segment and part of the FR2 region of the human Vβ8, has shown both an immunoregulating and immunostimulating effect in viral induced immunodeficient mice. In our study, 18 month-old C57Bl/6 female mice were treated twice with 200 μg of TCR Vβ8.1 peptide and 10 days before sacrificed they were i.p infected with Coxsackievirus B3. Cardiac histopathology was semi-quantitatively assessed for lesion severity and induced production cytokines from splenocytes: IL-2, -4, -6, IFN-γ and Coxsackievirus titers from heart were determined. Our data suggests that immunosenescence suppressed both TH1 and TH2 cytokine production and that treatment with TCR Vβ8.1 peptide induce cytokine stimulation close to levels seen in 14 week-old mice. Non-treated aged-mice developed some degree of myocarditits (75% mild and 25% severe). While only 35% of the peptide-treated aged group developed cardiopathology with 25% being mild and 10% severe. Hearts from non-treated aged mice infected with coxsackieviurs had a higher viral titer (up to 4 times more) than hearts of aged mice equally infected but treated with the peptide. In conclusion, TCR Vβ8.1 peptide induced immunstimulation and inhibited or reduced coxsackievirus B3 induced cardiopathology in aged mice.

INTRODUCTION

Immunosenescence is a gradual decline of the immune system's competence to maintain to host free of infection and cancer development. In humans as well as in animals the mechanisms of defense declines in direct proportion to ageing. Although both innate and adaptive arms of the immune systems are changed, the adaptive compartment is mostly affected. Innate immunity establishes immediately after birth and shows only slight changes throughout life. In difference, adaptive immunity is immature in neonates, optimal in young adults and progressively declines thereafter. In elderly humans, naïve T cells, total B cells and CD5+ B lymphocytes are decreased, whereas activated and memory T cells as well as NK marker CD56+ lymphocytes are expanded (Ginaldi, L., 2001). Aged mice, show decreased numbers of Thy 1+ cells in the thymus, a higher number of cells expressing IL-2R and lower number of IgA+ plasma cells in the intestinal lamina propria than younger mice (Colombo, L.L., 1999). In old mice T and B cell proliferation is reduced, while TNF-α, IL-4 and IL-6 are secreted more abundant as oppose to a decrease in IL-2 (Liang, B., 1998). We have previously reported that administration of TCR Vβ 8.1 peptide to old mice re-establishes cytokine production as well as B and T cell proliferation comparable to that of young mice (Liang, B., 1998).

We have previously reported that prophylactic administration of TCR Vβ 8.1, a CDR1 16-mer peptide, prior to murine retroviral infection, profoundly retarded the immune dysregulation otherwise found in murine AIDS (14). The peptide prevented suppression of natural killer (NK) cell activity, T- and B-cell proliferation, the release of IL-6, TNF-α and IFN-γ from splenocytes, and inhibited the elevation of IL-5 and IL-10, typically seen in this model of murine AIDS (15).

Coxsackievirus B3 (CVB3), can induce an inflammatory disease in the heart that results in cardiopathology in individuals with compromised immune systems. Certain inbred strains of mice, such as the C3H and BALB/C, are susceptible to the infection (16,17), while the C57BL/6 strain is resistant (18-20). However, we have previously shown that if the immune system is compromised, heart pathology will develop in mice that are normally resistant to infection. If the C57BL/6 strain is exposed to the CVB3 under immune compromising conditions such as retroviral infection, which can be exacerbated with sustained cocaine or alcohol use, the mice will develop heart disease (19,20). Similar, if aged mice are exposed to the viral pathogen under a sub-optimal immune condition as in immunosenescence, cardiopathology will develop.

The objective of this study is to determine if TCR Vβ8.1 peptide will promote immunestimulation sufficient to stop the development of cardiopathology due to CVB3 infection in aged mice.

MATERIAL AND METHODS

Peptides

A set of overlapping 16-mer peptides that duplicate covalent structure of the VßDßJßCß protein (22,23) predicted from a human TCR-Vß sequence has been produced (24). The complete range of peptide sequences was previously reported in detail (25). Here, we focus on the sequence C K P I S G H N S L F W Y R Q T that corresponds to the complete CDR1 and N-terminal five residues of Fr2 (22,25) of the human Vß8.1 gene product (10). As a control peptide, we used a 16-mer corresponding to the CDR1 of the L chain MCG (26), because healthy mice did not produce autoantibodies (Aab) to this peptide. Its sequence is T G T S S D V G G Y N Y V S W Y. The peptide preparations were free of endotoxins. We have shown previously that normal polyclonal IgG pools contain natural Aab against peptide segments corresponding to CDR1, Fr3, and a constant region loop peptide of the TCR Vβ-chain (22).

Coxsackievirus B3 infection

Cardiovirulent Coxsackievirus B3 serotype 59 stocks were propagated in HeLa cell monolayers in minimal essential medium supplemented with 10% fetal bovine serum and 50 mg/L gentamicin (GIBCO BRL, Gaithersburg, MD) at 37°C in a humidified 5% CO_2 atmosphere. Virus was titered by tissue culture infectious dose-50 ($TCID_{50}$) (16). After 3 months of retroviral infection, mice were inoculated intraperitoneally with 3×10^5 $TCID_{50}$ of CVB3 strain 59 in 0.1 ml of MEM. Mice were sacrificed after 12 days of CVB3 infection.

Histopathology

At indicated times after inoculation, mice were killed and their hearts removed for study. Hearts were rinsed in saline and transversely cut in half. One half of each heart was immediately placed into Histochoice Tissue Fixative (AMRESCO, Solon, OH, U.S.A.) and stored at room temperature. Fixated hearts were sectioned (6 μm) on a Zeiss HM 505 N cryostat (Carl Zeiss, Thornwood, NY, U.S.A.) and stained with hematoxylin and eosin. The severity of inflammatory lesions within the myocardium was graded by a pathologist without knowledge of the other experimental variables. Grading was performed in a semiquantitative manner according to the relative degree (from heart to heart) of mononuclear cell infiltration and the extent of necrosis. Mild damage is considered as <10% of heart tissue affected, moderate = 10-25% and severe as >25% of heart tissue affected.

Heart viral titers.

At the indicated times after inoculation, mice were sacrificed and one-half of the heart removed for viral titers. Heart halves were rinsed in saline and immediately frozen on dry ice and then stored at -80°C until processed. Heart sections were weighed, then ground in

a small volume of RPMI-1640 using a Ten Broeck homogenizer (Fisher Scientific) and freeze-thawed three times. The ground tissue was then centrifuged (2000 x g), and the resulting supernatant was recovered for assay. Supernatant was tittered on HeLa cell monolayers by $TCID_{50}$ (16).

RESULTS

Histopathology

Young or mature-healthy C57BL/6 mice (3-10 month old) do not develop cardiopathology when challenged with CVB3, although they become susceptible when immunodeficient due to LP-BM5 infection (19,20,28). To determine if TCR Vβ8.1 treatment would protect aged mice from developing cardiopathology due to CVB3 infection, C57BL/6 mice were infected with CVB3 at 18 months of age for 12 days. TCR Vβ8.1 or control peptides were administered at 1 week and 2 weeks before CVB3 infection. Aged mice co-infected with CVB3 and treated with the control peptide, developed cardiopathology with scores 1+ (25%), 2+ (50%) and 3+ (25%). However, when identically infected mice were treated with TCR Vβ 8.1 peptide, 18% of the group showed 1+ scores, 10% showed 2+ and only 9% showed a 3+ score, while 62% of them presented no pathology (Fig. **1**).

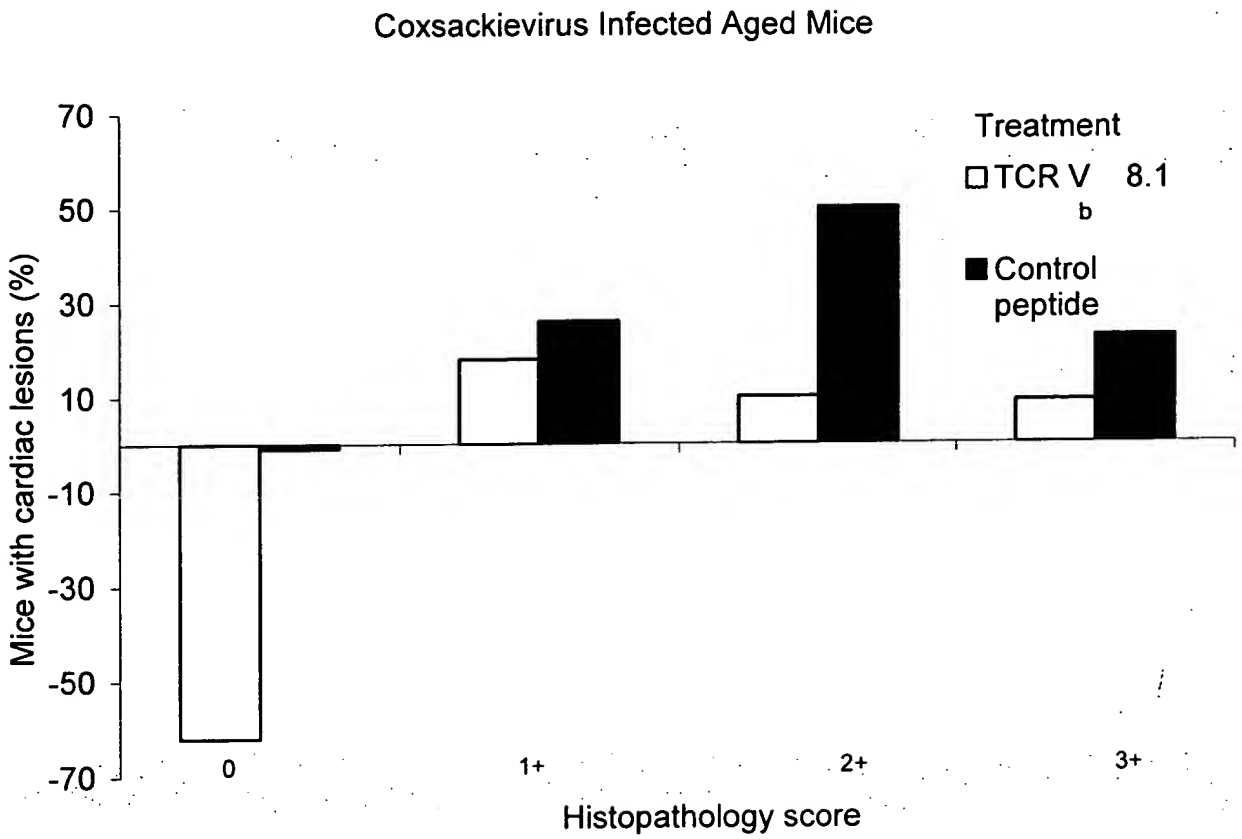

Fig. 1. Histopathologic scores of Aged-mice infected with CVB3/59 and treated with TCR Vβ8.1 peptide. Pathologic score: 0, no lesions; 1+, mild multifocal non-suppurative epicarditis to mild multifocal non-suppurative myocarditis; 2+, mild focal to multifocal non-suppurative myocarditis with myocardiocyte degeneration and necrosis; 3+, moderate focal to multifocal non suppurative myocarditis with myocardiocyte degeneration and necreosis; 4+, severe multifocal non-suppurative myocarditis with myocardiocyte degeneration and necrosis. Mild damage is considered as <10% of heart tissue affected, moderate = 10-25% and severe as >25% of heart tissue affected.

Viral titers

To determine whether the difference in cardiopathology between aged-mice infected with CVB3 + control peptide and aged-mice infected with CVB3 + TCR Vβ8.1 peptide was due to difference in the viral titer, we determined the geometric mean titers of virus recovered from the hearts of infected animals. Hearts from individual mice infected with

CVB3 were assayed for the presence of replicating virus in the tissue (Table 1). Heart from aged mice infected with CVB3 and treated with the control peptide, showed higher viral titers after 12 days of infection, than aged mice similarly infected and treated with the TCR Vβ8.1 peptide ($p<0.05$). All control aged-mice non-CVB3 infected and aged-mice treated with the TCR Vβ8.1 peptide showed no signs of pathology.

Table 1. Cardiac viral titers of CVB3/59 from heart-tissue of aged-mice treated with TCR Vβ8.1 peptide.

Treatment			Cardiac viral titer[a]
Control Peptide	TCR Vβ8.1 peptide	CVB3/59	$TCID_{50}$/g tissue
+	-	-	ND
-	+	-	ND
+	-	+	1.0×10^8 ($2.8 \times 10^7 - 5.4 \times 10^8$)
-	+	+	2.5×10^7 ($5.1 \times 10^6 - 7.5 \times 10^7$)[b]

[a] Heart viral titers are expressed as means of 8 to 10 mice, with the range in parentheses.
[b] Significantly different to the control group ($p<0.05$)
ND= Not Detectable

Cytokine Production by Splenocytes

To determine the effect on cytokine production of TCR Vβ8.1 peptide on aged-mice infected with CVB3, Th1 (IL-2, TNF-α and IFN-γ), IL-4 (Th2) and IL-6 cytokine production was assessed (Tables 2 and 3). Production of IFN-γ by Con A-stimulated splenocytes was significantly ($p<0.05$) inhibited in aged-mice infected with CVB3 when compared to the no CVB3 infected group. TCR Vβ8.1 peptide treatment significantly increased IL-2 and IFN-γ (2 fold) production in the CVB3 infected group, when compared to the control peptide treated animals ($p<0.05$), for the same groups, TNF-α showed no significant change (Table 2). Both humoral immne response promotor cytokines determined (IL-4 and IL-6) showed a significant decrease in there production in the TCR Vβ8.1 peptide treated group infected with CVB3, when compared to the control peptide treated animals ($p<0.05$).

Table 2. Effect of TCR Vβ8.1 treatment on Th1 cytokine production of aged-mice infected with Coxsackievirus B3.

Groups			Cytokines (ng/ml)		
Control Peptide	TCR Vβ8.1 peptide	CVB3/59	IL-2	IFN-γ	TNF-α
+	-	-	0.43±0.15	16.8±1.4	1.45±0.1
-	+	-	0.95±0.1	26.4±1.71	0.75±0.13
+	-	+	1.16±0.13	10.7 ±0.5	0.85±0.2
-	+	+	1.75±0.2	20.2±0.3	1.2±0.1

Splenocytes ($1x10^7$ cells/ml in RPMI medium) were incubated with Con A or LPS at 37°C. After collection of the supernatants, cytokines were determined using a Pirce-Endogen KM-minikits. The concentration of the cytokines were determined by ELISA at 450 nm. Data is presented as means (95 CI) of triplicate wells.

Table 3. Effect of TCR Vβ8.1 treatment on a Th2 and IL-6 cytokine production of aged-mice infected with Coxsackievirus B3.

Groups			Cytokines (ng/ml)	
Control Peptide	TCR Vβ8.1 peptide	CVB3/59	IL-4	IL-6
+	-	-	0.49±0.12	1.81±0.21
-	+	-	0.23±0.21	1.25±0.22
+	-	+	1.15±0.1	1.90±0.16
-	+	+	0.75±0.05	1.05±0.1

Splenocytes ($1x10^7$ cells/ml in RPMI medium) were incubated with Con A or LPS at 37°C. After collection of the supernatants, cytokines were determined using a Pirce-Endogen KM-minikits. The concentration of the cytokines were determined by ELISA at 450 nm. Data is presented as means (95 CI) of triplicate wells.

DISCUSSION

In animals as well as in humans, aging influences the competence of the immune system to maintain the hosts integrity against pathogens as well as its ability to control cancer cells at bay. Our results show that cytokine dysregulation due to immunosenescence affects mostly Th1 cytokine production, and that TCR Vβ8.1 peptide therapy will stimulate their secretion enough to have a capable cellular immune response against the development of severe myocarditis due to a cardiovirulent pathogen. Out of the three Th1 cytokines determined, IL-2 and IFN-γ seem to be the ones that are suppressed the most. TCR Vβ8.1 peptide administration to aged mice increased IL-2 cytokine production by two fold, when compared to the control peptide treated group (Table 2). Coxsackieviral infection by itself increased IL-2 production considerably when measured in control peptide treated animals, and TCR Vβ8.1 peptide administration for the same treatment group, enhanced IL-2 production (Table 2). IFN-γ production was suppressed after CVB3 infection in the control group, but treatment of TCR Vβ8.1 peptide to either CVB3 infected or non-CVB3 animals, increased its production even beyond the non-treated non-infected group (Table 2). Moreover, IFN-γ production by aged mice after TCR Vβ8.1 peptide treatment, specially in the non-CVB3 group, showed levels similar to those seen in young 14 week old mice (Data not shown). The production of both IL-2 and IFN-γ after TCR Vβ8.1 peptide treatment in aged mice, inversely correlate with the frequency as well as the severity of cardiopathology due to CVB3 infection (Figure 1) as well as with the presence of viral particles from heart muscle tissue (Table 1).

In conclusion, our results show an important immunostimulatory effect of TCR Vβ8.1 peptide in aged mice. The TCR Vβ8.1 peptide induced Th1 cytokine production which promotes a more capable cellular immune response and in turn protects the host against the development of myocarditis due to CVB3 infection. TCR Vβ8.1 peptide also promoted the clearance of CVB3 viral particles from heart muscle tissue. This study further supports the potential of TCR Vβ8.1 peptide therapy in host immunostimulation as well as in immuneregulation against viral and autoimmune diseases.

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